REMARKS

The undersigned gratefully acknowledges a telephone inteview given by the Examiner on March 25, 2005. During that conference, the Examiner indicated that he preferred to consider the present new claims as part of an RCE submission. The undersigned is happy to comply with this request. The undersigned also gratefully acknowledges the telephone interview given by the Examiner and his supervisor to her and to her colleague, Dr. Robert Buchanan, on January 19, 2005.

Further to the Letter submitted on March 25, 2005, and as discussed in the previous interview on January 19, 2005, it is Applicants' wish to have the instant invention considered in its entirety and without restriction to single peptide embodiments. See e.g., the Final Office Action dated December 14, 2005. It is understood that the Examiner and his supervisor agreed to consider this request in light of the attached new claims. Such consideration now is earnestly requested.

In the present Amendment, claim 56 has been amended, and new claims 74-81 have been added. Claims 1-55 and 57-73 have been canceled without prejudice. Applicants reserve the right to file an appropriate continuation or divisional application encompassing this subject matter. No new matter has been added.

Support for the amendments to claim 56 and for new claims 74-81 can be found throughout the instant disclosure including the claims as filed originally. Claim 56 has been amended to be dependent on new claim 74, rather than on canceled claim 44. More specific support for new claims 74-81 can be found, e.g., as outlined in Table A (below), as well as in the Examples (especially pages 31-48) and in the results shown in the corresponding Figures.

Table A

CLAIM(S)	EXEMPLARY SUPPORT
74-81	Page 8, line 17 – page 10, line 13 Page 12, lines 4-6 Page 12, line 12 – page 14, line 10 Page 17, line 4 – page 18, line 21 Page 31, lines 6-24
75, 77	Page 13, line 25 – page 14, line 10 Page 17, lines 10-13 Page 21, line 26 – page 22, line 4 Page 24, line 25 – page 25, line 8
76	Page 9, lines 1-7 Page 12, line 24 – page 13, line 2 Page 13, lines 17-23 Page 31, lines 7-24
78-81	Page 9, line 14 – page 10, line 13 Page 13, lines 9-15 Page 14, line 12 – page 15, line 11 Page 18, lines 23-28
80-81	Page 9, line 14 – page 10, line 13 Page 12, line 25 Page 14, line 12 – page 17, line 1 Page 18, line 23-28 Page 22, line 14 – page 23, line 14

I. Brief Summary of the Claimed Invention

It is believed that a brief Summary of the claimed invention would be helpful.

There is recognition in the field that formation of β-sheets during peptide synthesis causes many difficulties which reduce yields, for example. The present invention addresses the problem by providing a better way to build a peptide chain.

In particular, to make a peptide of interest, one selects an amino acid "pre-sequence" with a propensity to reduce or avoid β-sheet formation. See new claim 74, part b.

That pre-sequence is coupled to a support. Further amino acids are added to the pre-sequence, for example, to make the peptide of interest. See new claim 74, part b. An important benefit is a reduction, or in some cases elimination, of a propensity to form a β-sheet structure within the growing peptide chain.

Further embodiments of this method are encompassed by new claims 75-81 and include use of linkers and further particularity with respect to protecting labile amino acid side chains.

II. Information from Corresponding and Allowed European Application

During the prior telephone discussions, the Office indicated that it would be difficult to search the literature with respect to the claimed invention. To the assist the Office, Applicants submit herewith a copy of relevant sections of allowed EP Application No. 97939974.8-1223. Below is a list of materials provided to the Examiner.

Appendix A: Claims allowed in Europe.

Appendix B: Copy of 8 August 2002 Communication indicating art considered relevant by the European Examiner and basis for rejecting the claims. The art cited is of record in this case (IDS mailed July 11, 2003).

Appendix C: Copy of 28 May 2001 Communication indicating art considered relevant by the European Examiner and basis for rejecting the claims. The art cited is of record in this case (IDS mailed May 25, 2000).

Appendix D: PCT International Preliminary Examination Report. The art cited is of record in this case (IDS mailed May 25, 2000).

Accordingly, and especially with the materials of Appendices A-D in hand, it is believed that the Office should be able to perform its own search without undue burden and without restricting the claims to a single peptide.

III. Request For an Interview

To confirm that the Office requires no further information from Applicant, the undersigned requests a telephonic interview with the Examiner and his supervisor before the Office takes action on the merits.

IV. Conclusion

If discussion of any amendment or remark made herein would advance this important case to allowance, the Examiner is invited to call the undersigned as soon as convenient. An early reconsideration and notice of allowance are earnestly solicited.

Applicants hereby request a two-month extension of time for the Amendment and submit the requisite fee herewith. If, however, a petition for an additional extension of time is required, then the Examiner is requested to treat this as a conditional petition for an additional extension of time. Although it is not believed that any fee is required, in addition to the fee submitted herewith, to consider this submission, the Commissioner is hereby authorized to charge our deposit account no. 04-1105 should any fee be deemed necessary.

Respectfully submitted,

Date: April 22, 2005

Kathryn A. Piffat, Ph.D.

Kathryn A. Piffat, Ph.D. (Reg. No. 34,901)
Intellectual Property Practice Group of
EDWARDS & ANGELL, LLP
P.O. Box 55874
Boston, MA 02205
(617) 439-4444
(617) 439-4170 (fax)

Customer No. 21874

Claims:

1. A process for the production of peptides

$X\text{-}AA_1\text{-}AA_2$ …..$AA_n\text{-}Y$

wherein AA is an L- or D-amino acid residue,

X is hydrogen or an amino protective group, and

Y is OH, NH_2 and n is an integer greater than 2 by solid phase synthesis

wherein the C-terminal amino acid in the form of an N-α-protected, and if necessary side chain protected, reactive derivative is coupled to a solid support or a polymer optionally by means of a linker, subsequently N-α-deprotected, whereafter the subsequent amino acids forming the peptide sequence are stepwise coupled or coupled as a peptide fragment in the form of suitably protected reactive derivatives or fragments, wherein the N-α-protective group is removed following formation of the desired peptide and the peptide is cleaved from the solid support,

c h a r a c t e r i z e d in that the process further comprises:

selecting a pre-sequence comprising from 3 to 9 residues independently selected from native amino acids having a side chain functionality which is protected during the coupling steps and having a propensity factor $P\alpha > 0.57$ and a propensity factor $P\beta \leq 1.10$, the C-terminal part of said peptide comprising the pre-sequence; and

cleaving said pre-sequence from the formed peptide.

2. The process according to claim 1, wherein the amino acids in the pre-sequence are chosen from amino acids having a side chain functionality which is a carboxy, carboxamido, amino, hydroxy, guanidino, sulphide or imidazole group.

3. The process according to claim 2, wherein the amino acids forming part of the pre-sequence are independently selected from Lys, Glu, Asp, Ser, His, Asn, Arg, Met and Gln.

4. The process according to claim 3, wherein the amino acids are either exclusively Lys or Glu or a sequence (Glu)q(Lys)p, where p + q is 3 to 9, preferably 6 to 9, and the order of Lys and Glu is arbitrarily chosen.

5. The process according to claim 1, wherein the N-α amino protective group is Fmoc, Boc or any other suitable protective group.

6. The process according to claim 5, wherein the N-α-amino protective group is Fmoc or Boc.

7. The process according to claim 1, wherein the side chain functionality in the pre-sequence comprises a carboxy group, which is suitably protected, preferably with tBu.

8. The process according to claim 1, wherein the side chain functionality in the pre-sequence comprises an amino group, which is suitably protected, preferably with Boc.

9. The process according to claim 1, wherein the side chain functionality in the pre-sequence comprises a hydroxy group, which is suitably protected preferably with tBu.

10. The process according to claim 1, wherein the side chain functionality in the pre-sequence comprises a carboxamido group protected with a) benzhydryl, b) trityl, c) tBu.

11. The process according to claim 1, wherein the side chain functionality in the pre-sequence comprises a guanidino group protected with 4-methoxy-2,3,6-trimethylphenylsulfonyl (Mtr), 2,2,5,7,8-pentamethylchroman-6-sulfonyl (Pmc) or 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl (Pbf).

12. The process according to claim 1, wherein the side chain functionality in the pre-sequence comprises an imidazole group protected with Boc.

13. The process according to claim 5, wherein the Fmoc groups are deprotected by means of an amine such as piperidine or diazabicyclo[5,4,0]undec-7-ene (DBU).

14. The process according to claim 1, wherein the side chain protective groups are deprotected by means of an acid such as trifluoroacetic acid (TFA), trifluoromethanesulfonic acid (TFMSA), HBr, HCl or HF.

15. The process according to claim 1, wherein the solid support is selected from functionalized resins such as

polystyrene, polyacrylamide, polyethyleneglycol, cellulose, polyethylene, latex or dynabeads.

16. The process according to claim 15, wherein the functionalized resins are selected from PEG-PS (polyethylene glycol grafted on polystyrene) or polydimethylacrylamide resins.

17. The process according to claim 1, wherein the pre-sequence comprises from 5 to 7 amino acid residues.

18. The process according to claim 15, wherein the C-terminal amino acid is attached to the solid support by means of a common linker such as 2,4-dimethoxy-4'-hydroxy-benzophenone, 4-(4-hydroxymethyl-3-methoxyphenoxy)-butyric acid (HMPB), 4-hydroxymethylbenzoic acid, 4-hydroxymethylphenoxyacetic acid (HMPA), 3-(4-hydroxymethylphenoxy)propionic acid or p-[(R,S)-a[1-(9H-fluoren-9-yl)-methoxyformamido]-2,4-dimethoxybenzyl]-phenoxyacetic acid (AM).

19. The process according to claim 1, wherein the synthesis is carried out batchwise.

20. The process according to claim 1, wherein the process is carried out continuously on an automated or semi automated peptide synthesizer.

21. The process according to claim 1, wherein the coupling steps are performed in the presence of a solvent selected from acetonitrile, N,N-dimethylformamide (DMF), N-methylpyrrolidone (NMP), dichloromethane (DCM), trifluoroethanol (TFE), ethanol, methanol, water,

mixtures of the mentioned solvents with or without additives such as perchlorate or ethylenecarbonate..

22. The process according to claim 1, wherein the coupling between two amino acids, an amino acid and the earlier formed peptide sequence or a peptide fragment and the earlier formed peptide sequence is carried out according to usual condensation methods such as the azide method, mixed acid anhydride method, symmetrical anhydride method, carbodiimide method, active ester method such as pentafluorophenyl (Pfp), 3,4-dihydro-4-oxobenzotriazin-3-yl (Dhbt), benzotriazol-1-yl (Bt), 7-azabenzotriazol-1-yl (At), 4-nitrophenyl, N-hydroxysuccinic acid imido esters (NHS), acid chlorides, acid fluorides, in situ activation by O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), O-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), O-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), or benzotriazolyl-oxy-tris-(dimethylamio)-phosphonium hexafluorophosphate (BOP).

23. The process according to claim 1, wherein the peptide is cleaved from the support by means of an acid such as trifluoroacetic acid (TFA), trifluoromethanesulfonic acid (TFMSA), hydrogen bromide (HBr), hydrogen chloride (HCl), hydrogen fluoride (HF) or a base such as ammonia, hydrazine, an alkoxide or a hydroxide.

24. The process according to claim 1, wherein the peptide is cleaved from the support by means of photolysis.

25. The process according to claim 1, wherein the pre-sequence is enzymatically cleaved from the formed peptide.

26. The process according to claim 24, wherein the enzyme is selected from suitable carboxy- and endopeptidases.

EPA/EPO/OEB
D-80298 München
+49 89 2399-0
TX 523 656 epmu d
FAX +49 89 2399-4465

Europäisches Patentamt	European Patent Office	Office européen des brevets
Generaldirektion 2	Directorate General 2	Direction Générale 2

Kiddle, Simon John
Mewburn Ellis,
York House,
23 Kingsway
London WC2B 6HP
GRANDE BRETAGNE

Telephone Numbers:	Branch at The Hague
Primary Examiner (substantive examination)	+31 70 340-4023
Formalities Officer / Assistant (Formalities and other matters)	+31 70 340-2360

Application No.	Ref.	Date
97 939 974.8-1223	SJK/FP5924824	08.08.2002
Applicant: Zealand Pharma A/S		

Communication pursuant to Article 96(2) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(1) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 78(2) and 83(2) and (4) EPC.

One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (Rule 36(1) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Article 96(3) EPC).

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SCHMIDT H M
Primary Examiner
for the Examining Division

Enclosure(s): 3 page/s reasons (Form 2906)
D2: Rapp & Bayer, 1994
D3: Merrifield, 1986

Registered Letter

The examination is being carried out on the **following application documents**:

Text for the Contracting States:
AT BE CH LI DE DK ES FI FR GB GR IE IT LU MC NL PT SE

Description, pages:

1-10,12-14,17-23, 26-56	as originally filed			
11,15,16,24,25	as received on	21.01.2002	with letter of	16.01.2002

Claims, No.:

1-30	as received on	21.01.2002	with letter of	16.01.2002

Drawings, sheets:

1/3-3/3	as originally filed

The following documents (D) are cited by the examiner (see the Guidelines, C-VI, 8.9). Copies of the documents are annexed to the communication and the numbering will be adhered to in the rest of the procedure:

D2: Rapp WE & Bayer E in: Hodges RS & Smith JA, Peptides- Chemistry, Structure and Biology. Proceedings of the 13th Annual American Peptide Symposium, published by ESCOM, Leiden, 1994

D3: Merrifield B (1986) Science 232: 341-347

1 Amendments

The amendments filed with your letter dated 16.01.2002 are in accordance with Article 123(2) EPC since no supplementary subject-matter has been added. With respect to the propensity factor Pβ, it is obvious from the amino acids listed

on page 16, lines 24/25 that Pβ should be ≤1.10.

2 Novelty

After reconsidering subject-matter of claims 1-30, objections against novelty have arisen.

2.1 Subject-matter of present claims 1 and 27 comprises the synthesis of peptides using the solid-phase peptide synthesis approach (also known as Merrifield synthesis, see for e.g. document D3) wherein the C-terminal has at least three amino acid residues selected from Ala, Lys, Glu, Asp, Ser, His, Asn, Arg, Met and/or Gln.
There are numerous documents that discloses the solid phase synthesis of peptides comprising such amino acid residues in their C-terminus, for illustration purpose see D2 disclosing the solid phase synthesis of H1c sequence 196-220 having three lysine residues at the C-terminus.
Therefore, subject-matter of claims 1 and 27 does not meet the requirements of Articles 52(1), 54(1) and (2) EPC.

2.2 Dependent claims 2-26 and 28-30 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the EPC with respect to novelty as such features are common general knowledge as set out in e.g. D3.

3 Clarity and Conciseness

3.1 It is unclear in the sense of Article 84 EPC whether the corresponding D-amino acids may also be used as presequences since only the L-amino acids appear to have suitable propensity factors (see page 23-25).

3.2 Claims 11,25 and 26 are not supported by the description as required by Article 84 EPC, as their scope is broader than justified by the description and drawings. The reasons therefor are the following:

(a) the protecting groups of claim 11 are mentioned in the claims as published (claim 11), but are not sufficiently supported by the description;
(b) the description does not teach an enzymatic cleavage of the presequence from the formed peptide; however, the claims as published (claims 28 and 29) discloses such an approach.

4 Rule 88 EPC

The Applicant is invited to correct "Dnbt" to "Dhbt" (see claim 22, line 9) as it is obvious from page 27, lines 24/25).

5 Conclusions

The Applicant is requested to file a new set of claims and adapt the description to subject-matter of the new claims.

EPA/EPO/OEB
D-80298 München
+49 89 2399-0
TX 523 656 epmu d
FAX +49 89 2399-4465

Europäisches Patentamt	European Patent Office	Office européen des brevets
Generaldirektion 2	Directorate General 2	Direction Générale 2

Kiddle, Simon John
Mewburn Ellis,
York House,
23 Kingsway
London WC2B 6HP
GRANDE BRETAGNE

Telephone Numbers:	Branch at The Hague
Primary Examiner (substantive examination)	+31 70 340-4023
Formalities Officer / Assistant (Formalities and other matters)	+31 70 340-2360

Application No.	Ref.	Date
97 939 974.8-1223	SJK/FP5924824	28.05.2001
Applicant: Zealand Pharmaceuticals A/S		

Communication pursuant to Article 96(2) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(1) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 78(2) and 83(2) and (4) EPC.

Amendments to the description, claims and drawings are to be filed where appropriate within the said period in **three copies** on separate sheets (Rule 36(1) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Article 96(3) EPC).

SCHMIDT H M
Primary Examiner
for the Examining Division

Enclosure(s): 3 page/s reasons (Form 2906)

Registered Letter

The examination is being carried out on the **following application documents**:

Text for the Contracting States:
AT BE CH LI DE DK ES FI FR GB GR IE IT LU MC NL PT SE

Description, pages:

1-56 as originally filed

Claims, No.:

1-20 as received on 25.03.1999 with letter of 25.03.1999

Drawings, sheets:

1/3-3/3 as originally filed

1 The following **documents** are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: US 5021550 A (04.06.1991)

2 **AMENDMENTS** (Art. 123 EPC)

2.1 The present application does not meet the requirements of Article 123(2) EPC, because some amendments filed with your letter dated 25.03.1999 extend beyond the content of the application as originally filed. The amendments are the followings:

1. The whole subject-matter of claim 20
2. The term "trihydrogen bromide" in claim 12

No basis in the application as originally filed could be found for these amendments. To overcome the objections mentioned above the applicant should:

1. suppress the whole subject-matter of claim 20
2. replace "trihydrogen bromide" by "hydrogen bromide (HBr)" as originally filed (see original claim 27)

2.2 No opinion on novelty and inventive step on claim 20 will be given.

3 NOVELTY (Art. 54 EPC)

3.1 In view of the prior art cited, claims 1-19 are novel and do therefore meet the requirements of Article 54 EPC.

3.2 D1 discloses a method for solid-state synthesis of polymers which comprises intermediate polypeptides reacting with an amino acid moiety. Intermediate polypeptides which have successfully reacted with amino acid moieties are bound to the solid support only through the terminal amino acid residue. Unreacted intermediate polypeptides become covalently bound to the solid support in at least two location, thus are "cyclized". There are no hints that the intermediate peptides in D1 comprise 3 to 9 amino acids which have the propensity factors as mentioned for the presequence in claim 1. Subject-matter of the independant product claims 16-19 is also based on the presequence of claim 1.

4 INVENTIVE STEP (Art. 56 EPC)

4.1 Document D1 is considered to represent the most relevant state of the art and discloses an improved method of preparing polypeptides using a preselected polypeptide intermediate, wherein unreacted intermediates are attached to their supports at two locations and are thus removed from further reactions and from the final reaction product to achieve highly pure polypeptides by preventing deletion sequences (cf. D1, page 3, lines 61-68). The subject-matter of claim 1 differs in that a presequence comprises 3 to 9 amino acid residues wherein the amino acids have a propensity factor P(alpha) > 0.57 and a propensity factor P (beta) > 1.10.

4.2 The problem to be solved by the present invention may therefore be regarded as providing an improved method for achieving peptides with of high yield and purity. The proposed solution is a process using presequences comprising 3 to 9 amino acid residues wherein the amino acids have a propensity factor P(alpha) > 0.57 and a propensity factor P (beta) > 1.10.

4.3 To use said presequences to solve the problem does not appear to be obvious for the skilled person. Therefore, claim 1 and independant claims 16-19 involve an inventive step in the sense of Article 56 EPC.

5 MINOR OBJECTIONS

5.1 To meet the requirements of Rule 27(1)(b) EPC, document D1 should be identified in the description and the relevant background art disclosed therein should be briefly discussed.

5.2 Introduction of "a" in claim 2: "....functionality which is **a** carboxy....."

5.3 "R" in the formula in claim 10 should be "R^2" as it is obvious from the description (see p. 23, formula) in accordance with Rule 88 EPC.

5.4 Introduction of "an" in claim 12: "....by means of **an** acid.....

6 CONCLUSIONS

The applicant is requested to file new claims which take account of the above comments.

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F 19

PATENT COOPERATION TREATY

01. 10. 1998 **PCT**

REC'D 17 SEP 1998
WIPO

5

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P199600050 WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/DK97/00375	International filing date *(day/month/year)* 09.09.1997	Priority date *(day/month/year)* 09.09.1996
International Patent Classification (IPC) or national classification and IPC6 C 07 K 1/04		
Applicant Holm, Arne et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07.04.1998	02.09.1998
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88	Authorized officer Carolina Palmcrantz Telephone No. 08-782 25 00

Telex 17979 PATOREG-S

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/DK97/00375

I. Basis of the report

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitatic under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

☒ the international application as originally filed.

☐ the description, pages _____, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____

☐ the claims. Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos _____, filed with the demand,
Nos. _____, filed with the letter of _____,
Nos. _____, filed with the letter of _____.

☐ the drawings, ~~sheets~~/fig _____, as originally filed,
~~sheets~~/fig _____, filed with the demand
~~sheets~~/fig _____, filed with the letter of _____.
~~sheets~~/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, ~~sheets~~/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/DK97/00375

V. Resoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-39	YES
	Claims		NO
Inventive step (IS)	Claims	1-39	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-39	YES
	Claims		NO

2. Citations and explanations

The present application pertains to a process and to an agent for the production of peptides by solid-phase synthesis (SPPS). The C-terminal part of the peptide which is attached to the solid support comprises a pre-sequence of 3 to 9 amino acid residues. The amino acid residues are selected from native L-amino acids having a side chain functionality which is protected during the coupling steps and having a propensity factor Pα higher than 0.57 and a propensity factor Pβ higher than 1.10 or the corresponding D-amino acids.

By incorporating a pre-sequence, having particular conformational parameters, at the C-terminus coupling times are reduced and incomplete peptide bond formation is avoided.
Thus, by practising the method according to the present application 'difficult sequences' (sequences to which incomplete couplings are more prevalent) can be produced in high yield and purity.

The International Search Report revealed one document of interest:

A) US, A, 5021550

Document A discloses a method for preventing deletion sequences in solid phase synthesis of , e.g., polypeptides by providing an intermediate polypeptide covalently bound to a solid support. The intermediate polypeptide is then covalently bound to an amino acid moiety. Intermediate polypeptides which have successfully reacted with a further amino acid moiety remain bound to the solid support while unreacted intermediate polypeptides become covalently bound or otherwise attached to the solid support in at least two locations, i.e. they become 'cyclized'.

../..

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

Therefore, in view of document A it is not considered to be obvious to a person skilled in the art to solve the problem of incomplete peptide bound formation by using an intermediate polypeptide or pre-sequence of 3 to 9 amino acid residues and having a propensity factor Pα higher than 0.57 and a propensity factor Pβ higher than 1.10.

Thus, claims 1-39 are considered to fulfil the requirements of novelty, inventive step and industrial applicability.